REMARKS

Claims 1, 3, 4, 6 to 8, 11 to 16 and 18 to 22, and new Claims 23 to 27 are present.

Claim 5 has been cancelled.

New Claims 23 to 27 have been added.

Claims 1 to 6, 12 to 16 and 21 to 22 are rejected under 35 U.S.C. §112, first paragraph.

Claims 1 to 5, 7 to 8 and 10, 14, 18 and 21 to 22 are rejected under 35 U.S.C. §103(a).

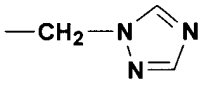
Claim 17 is objected to.

Amendments

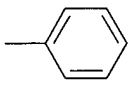
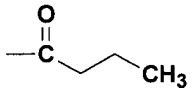
Basis for the present amendments can be found in the original claims and throughout the examples as originally filed. No new matter has been added. The scope of the claims has not been broadened by these amendments.

Claim 1 has been amended to limit R_8 and R_9 to alkyl substituted with heteroaryl, cycloalkyl, aryl, or $-C(=O)R_{13}$ where R_{13} is alkyl.

New Claim 23 defines one of R_8 and R_9 as alkyl substituted with heteroaryl and the other as cycloalkyl.

New Claim 24 defines one of R_8 and R_9 as  and the other as cyclohexyl.

New Claim 25 defines one of R_8 and R_9 as aryl and the other as or $-C(=O)R_{13}$ where R_{13} is alkyl.

New Claim 26 defines one of one of R_8 and R_9 as  and the other as  .

New Claim 27 defines the compounds of Examples 86 and 90.

Basis for the above amendments is found in Claims 1 and 17 as filed and in the working Examples 1 to 84, 86 and 89 to 323.

As suggested by the Examiner, the claims have been amended to delete R_8 and R_9 forming a spiro ring as being directed to a non-elected invention according to the Examiner. Applicants reserve the right to file a divisional application to cover the spiro compounds formed by taking R_8 and R_9 together.

With respect to the rejection based on the term "wherein two . . . are joined to form a fused ring", as discussed in the previous amendment, Applicants believe that ample information is given

in the Specification to enable one of skill in the art to identify appropriate starting materials. Applicants do not understand the Examiner's rejection that "[o]ne skilled in the art may be able to make the compounds *if one knows what it is*".

The Examiner's objection to "R_{13}-R_{14} or R_{14}-R_{15} forms a fused ring is no longer applicable since the compounds claimed no longer include an R_{14} moiety.

The Examiner has maintained the rejection of claims 21-22 under 35 U.S.C §112 in spite of Applicants amending the claims in response to her rejection. The Examiner has then imposed a new rejection under 35 U.S.C. §101 with respect to the phrase "treating a melanocortin receptor associated condition". The Examiner contends that the claim is confusing as to whether the method is on receptor function or on treating a disorder and states that "mere manipulation without effect is not within the scope of 'use'." Applicants traverse.

As stated in the Specification, page 43, lines 16-19, "the inventive compounds exemplified herein ha[ve] been tested and show activity at a measurable level for modulating a melanocortin receptor according to an assay described below and/or an assay known in the field, such as, for example, assays described in WO 00/74679 and WO 01/91752." Credible (recognized in the art) utilities for compounds that modulate melancortin receptors are cited in the Specification, pages 34 through paragraph one on page 37. Accordingly, Applicants request withdrawal of the new rejection under 35 U.S.C. §101.

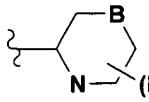
Also, as evidenced in the many references cited throughout the Specification, it is well known in the art that melanocortin receptor associated conditions may be treated by compounds which modulate melanocortin receptors, such as those of the present invention. Accordingly, Applicants assert that based on what is known in the art and the information given in the specification, one of skill in may treat melanocortin receptor associated conditions.

Claim 21 has been amended as suggested by the Examiner to include the phrase "A method of treating a disease or disorder treatable by melanocortin receptor agonism comprising administering melanocortin receptor agonistic effective amount . . ." Claim 21 as amended is essentially of the same scope as Claim 21 as filed.

Rejections under 35 U.S.C. §102(a)

The Examiner alleges that the rejection of Claims 1-2, 4-5, 10, 14, 18 and 21-22 under 35 U.S.C. §102(e) over Palucki has been dropped in view of the amendment requiring that y is at least 1. Applicants want to emphasize that the variable "y" has NOT been so amended.

However, Applicants have amended the claims so that W does not include



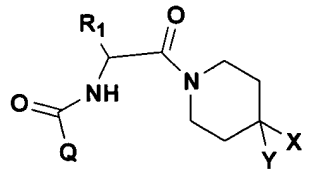
, wherein B is N, O or S. Basis can be found throughout the examples. Applicants believe that the claims, as now amended, renders the rejection for anticipation over Palucki moot.

Rejections under 35 U.S.C. §103(a)

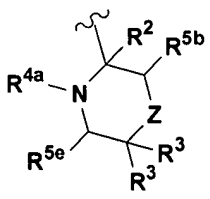
The Examiner has maintained the rejection of Claims 1-2, 4-5, 10, 14, 18 and 21-22 under 35 U.S.C. §103(a), as being obvious over U.S. 6,458,790 ("Palucki") for the "reasons of record" recommending that the claims be amended to maintain consistency in the y variable (i.e. y is at least 1). The Examiner further contends that "to the extend that y is at least 1, then the claims are still drawn to the 1-methylene inserted compounds of the prior art which are considered structural prima facie in absence-of unexpected result."

First, as discussed above, "y" has not been amended in the claims. The "y" variable definition is consistent in claim 1. There is merely a proviso in the definition of R_{11} in which R_{11} is not heterocyclo or heterocycloalkyl when y is 0.

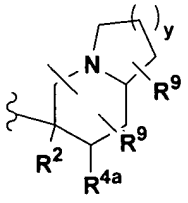
Secondly, Applicants amended claims describe compounds that are not simply a 1-methylene inserted variation of the Palucki compounds. Palucki's compounds are represented by the following generic structure:



where Q is a heterocyclo ring having the specific core structure



or



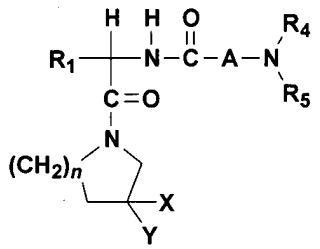
where Z is O, S or NR (See Palucki, column 5, lines 58-65).

None of Applicants' amended claims contain the heterocyclo rings described by the Q variable of the Palucki compounds. Nor does Palucki describe or suggest the unexpected desirability of Applicants' claimed compounds. Palucki actually teaches away from Applicants claimed compounds as one of skill in the art would only expect desirable activity from compounds

having the aforementioned Q group heterocycles. Moreover, Palucki specifies that their particularly described heterocycles be directly attached to a carbonyl. Applicants claimed compounds are substantially different from the Palucki compounds as they do not include the Palucki heterocycles ("Q"), nor do they describe any heterocycle directly attached to the carbonyl. Accordingly, Applicants request withdrawal of the obviousness rejection under 35 U.S.C. §103(a) over Palucki.

The Examiner again rejected claims 1-5, 7-8, and 10-16 under 35 U.S.C. §103(a) over U.S. 5,622,973 ("Morriello") in view of U.S. 6,303,620 ("Hansen") for the "reasons of record". Applicants ask the Examiner to reconsider this rejection.

U.S. Patent No. 5,622,973 to Morriello discloses compounds of the structure



wherein:

X is selected from: hydrogen, –C–N, $-(CH_2)_qN(R_2)C(O)R_2$, $-(CH_2)_qN(R_2)C(O)(CH_2)_t$aryl, $-(CH_2)_qN(R_2)SO_2(CH_2)_t$aryl, $-(CH_2)_qN(R_2)SO_2R_2$, $-(CH_2)_qN(R_2)C(O)N(R_2)(CH_2)_t$aryl, $-(CH_2)_qN(R_2)C(O)N(R_2)(R_2)$, $-(CH_2)_qC(O)N(R_2)(R_2)$, $-(CH_2)_qC(O)N(R_2)(CH_2)_t$aryl, $-(CH_2)_qC(O)OR_2$, $-(CH_2)_qC(O)O(CH_2)_t$aryl, $-(CH_2)_qOR_2$, $-(CH_2)_qOC(O)R_2$, $-(CH_2)_qOC(O)(CH_2)_t$aryl, $-(CH_2)_qOC(O)N(R_2)(CH_2)_t$aryl, $-(CH_2)_qOC(O)N(R_2)(R_2)$, $-(CH_2)_qC(O)R_2$, $-(CH_2)_qC(O)(CH_2)_t$aryl, $-(CH_2)_qN(R_2)C(O)OR_2$, $-(CH_2)_qN(R_2)SO_2N(R_2)(R_2)$, $-(CH_2)_qS(O)_mR_2$, and $-(CH_2)_qS(O)_m(CH_2)_t$aryl, where an R_2, $(CH_2)_q$ and $(CH_2)_t$ group may be optionally substituted by 1 to 2 C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl, naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be optionally substituted by 1 to 3 halogen, 1 to 3 $-OR_2$, $-CON(R_2)(R_2)$, $-C(O)OR_2$, 1 to 3 C_1-C_4 alkyl, $-S(O)_mR_2$, or 1H-tetrazol-5-yl;

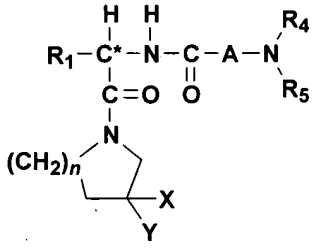
Y is selected from: hydrogen, C_1-C_{10} alkyl, $-(CH_2)_t$aryl, $-(CH_2)_q(C_3$-$C_7)$ cycloalkyl), $-(CH_2)_q$–K–(C_1-C_6 alkyl), $-(CH_2)_q$–K–$(CH_2)_t$aryl, $-(CH_2)_q$–K–$(CH_2)_t(C_3$-C_7 cycloalkyl containing O, NR_2 S), and $-(CH_2)_q$–K–$(CH_2)_t(C_3$-C_7 cycloalkyl), where K is O, $S(O)_m$,

$C(O)NR_2$, CH=CH, $C\equiv C$, $N(R_2)C(O)$, $C(O)NR_2$, C(O)O, or OC(O), and where the alkyl, R_2, $(CH_2)_q$ and $(CH_2)_t$ groups may be optionally substituted by C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $-CONH_2$ or carboxylate C_1-C_4 alkyl esters, and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrazinyl, or isothiazolyl which is optionally substituted by 1 to 3 halogen, 1 to 3 $-OR_2$, $-C(O)OR_2$, $C(O)N(R_2)(R_2)$, nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, $S(O)_mR_2$, or 1H-tetrazol-5-yl, with the proviso that if X is hydrogen, Y is other than hydrogen;

R_2 is selected from: hydrogen, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring, optionally including oxygen, sulfur or NR_{3a}, where R_{3a} is hydrogen, or C_1-C_6 alkyl, optionally substituted by hydroxyl;

m is 0, 1 or 2;
n is 1, 2, or 3;
q is 0, 1, 2, 3, or 4;
t is 0, 1, 2, or 3.

Preferred compounds of Morriello (as disclosed in Columns 4 and 5) include those of Formula 1a:



Formula Ia

wherein:

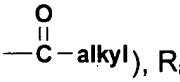
X is selected from: hydrogen, $-(CH_2)_qN(R_2)C(O)R_2$, $-(CH_2)_qN(R_2)C(O)(CH_2)_t$aryl, $-(CH_2)_qN(R_2)C(O)OR_2$, $-(CH_2)_qN(R_2)SO_2(CH_2)_t$aryl, $-(CH_2)_qN(R_2)SO_2R_2$, $-(CH_2)_qN(R_2)C(O)N(R_2)(CH_2)_t$aryl, $-(CH_2)_qN(R_2)C(O)N(R_2)(R_2)$, $-(CH_2)_qC(O)N(R_2)(R_2)$, $-(CH_2)_qC(O)N(R_2)(CH_2)_t$aryl, $-(CH_2)_qC(O)OR_2$, $-(CH_2)_qC(O)O(CH_2)_t$aryl, $-(CH_2)_qOC(O)R_2$,

$-(CH_2)_qOC(O)(CH_2)_t$aryl, $-(CH_2)_qS(O)_m(CH_2)$, where an R_2 group may be optionally substituted by hydroxyl, carboxyl, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or tetrazol, and aryl is phenyl, naphthyl, pyridyl or 1H-tetrazolyl which may be optionally substituted by 1 to 2 halogen, 1 to 2 $-OR_2$, $-CONH_2$, $-C(O)OR_2$, 1 to 3 C_1-C_4 alkyl, $-S(O)_mR_2$, or 1H-tetrazole-5-yl;

Y is selected from: hydrogen, C_1-C_8 alkyl, $-(CH_2)_t$aryl, $-(CH_2)_q(C_5$-$C_6)$ cycloalkyl, $-(CH_2)_q-K-(C_1$-C_6 alkyl), $-(CH_2)_q-K-(CH_2)_t$aryl, $-(CH_2)_q-K-(CH_2)_t(C_3$-C_7 cycloalkyl containing O, NR_2 S), and $-(CH_2)_q-K-(CH_2)_t(C_5$-C_6 cycloalkyl), where K is O or $S(O)_m$ and where the alkyl groups may be optionally substituted by hydroxyl, carboxyl, $CONH_2$, carboxylate C_1-C_4 alkyl esters or 1-H-tetrazole-5-yl and aryl is phenyl, naphthyl, pyridil, 1-H-tetrazolyl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiopheneyl which is optionally substituted by 1 to 3 halogen, 1 to 3 $-OR_2$, $-C(O)OR_2$, $C(O)N(R_2)(R_2)$, cyano, 1 to 2 C_1-C_4 alkyl, benzyl, $S(O)_mR_2$, or 1H-tetrazol-5-yl, with the proviso that if X is hydrogen, Y is other than hydrogen.

Please note that in the preferred Morriello et al. compounds X is not $-(CH_2)_qC(O)R_2$.

Although X can be $-(CH_2)_qC(O)R_2$, in fact, in the entire 148 columns of the Morriello patent only two ketones are disclosed for X, namely

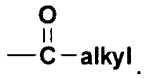
Morriello et al.'s compounds include X and Y at the 3-position of the piperidine whereas in Applicants' compounds, where one of R_8 and R_9 is ketone, the ketone (which is 

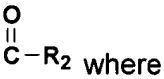
), R_8 and R_9 are at the 4-position.

In addition, please note that the Morriello et al. X substituent includes 23 substituents, 21 of which may or may not include an alkylene chain, while the Y substituent includes some 8 substituents, 6 of which may or may not include an alkylene group.

In Applicants' compounds as now claimed, one of R_8 and R_9 is alkyl substituted with heteroaryl and the other is cycloalkyl. None of the X groups of Morriello includes alkyl substituted with heteroaryl or cycloalkyl. Accordingly, Morriello does not disclose or suggest such compounds.

In Applicants' compounds as now claimed, one of R_8 and R_9 is aryl and the other is



None of Morriello's X groups includes aryl. Morriello's X groups include  where R_2 is H, alkyl or cycloalkyl and Morriello's Y group can be aryl. However, the only ketones actually disclosed by Morriello are  and  , neither of which is covered in Applicants' definition of R_8 and R_9.

In essence, Morriello includes at least 184 different possibilities for X and Y, none of which cover where X or Y is alkyl substituted with heteroaryl and the other is cycloalkyl (which is claimed in Claim 1 by Applicants).

Morriello includes at least 184 possibilities and for X and Y but does not disclose a single ketone except

 , and

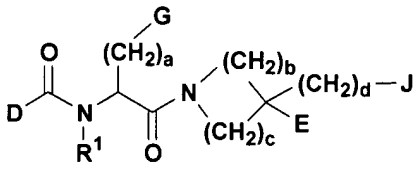
 ,

whereas Applicants claim one of R_8 and R_9 must be  alkyl, still, Morriello does not disclose or suggest a single example of such ketone or how to make a compound with such ketone.

Morriello et al. discloses a galaxy of possibilities for compounds, all of which include X and Y at the 3-position of the piperidine. One skilled in the art reading Morriello would have no motivation to come up with or prepare Applicants' compounds which is substituted with R_8 and R_9 at the 4-position of the piperidine as now claimed absent the use of hindsight in view of Applicants' disclosure.

In view of the foregoing it is submitted that Applicants' compounds as now claimed are patentable over Morriello et al.

Hansen et al. U.S. Patent No. 6,303,620 discloses compounds of the structure



wherein

R^1 is hydrogen, or C_{1-6}–alkyl optionally substituted with one or more aryl or hetaryl;

a and d are independently of each other 0, 1, 2 or 3;

b and c are independently of each other 0, 1, 2, 3, 4 or 5, provided that b+c is 3, 4 or 5,

D is

$$R^2–NH–(CR^3R^4)_e–(CH_2)_f–M–(CHR^5)_g–(CH_2)_h–$$

wherein R^2, R^3, R^4 and R^5 are independently hydrogen or C_{1-6} alkyl optionally substituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or

R^2 and R^3 or R^2 and R^4 or R^3 and R^4 may optionally form $–(CH_2)_i–U–(CH_2)_j–$, wherein i and j are independently 1 or 2 and U is –O–, –S– or a valence bond;

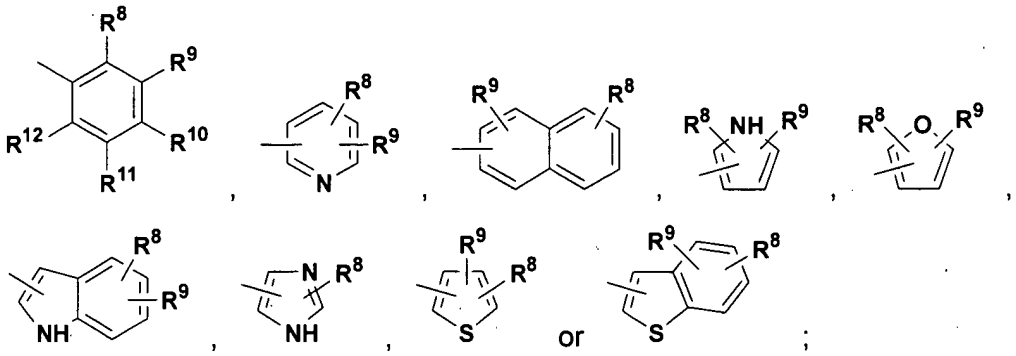
h and f are independently 0, 1, 2, or 3;

g and e are independently 0 or 1;

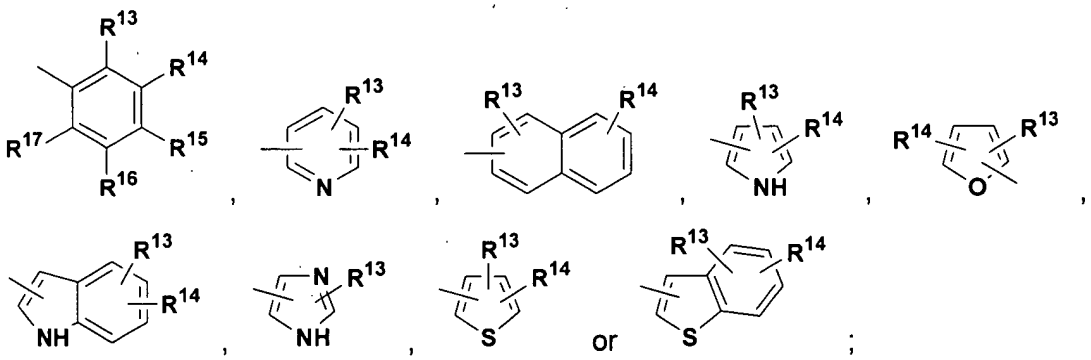
M is a valence bond, $–CR^6=CR^7–$, arylene, hetarylene, –O– or –S–;

R^6 and R^7 are independently hydrogen, or C_{1-6}alkyl optionally substituted with one or more aryl or hetaryl;

G is $–O–(CH_2)_k–R^8$,



J is $-O-(CH_2)_l-R^{13}$,



wherein R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} independently of each other are hydrogen, halogen, aryl, hetaryl, C_{1-6}–alkyl or C_{1-6}–alkoxy; k and l are independently 0, 1 or 2;

E is $-CONR^{18}R^{19}$, $-COOR^{19}$, $-(CH_2)_m-NR^{18}SO_2R^{20}$, $-(CH_2)_m-NR^{18}COR^{20}$, $-(CH_2)_m-OR^{19}$, $-(CH_2)_m-OCOR^{20}$, $-(CH)R^{18}R^{19}$, $-(CH_2)_m-NR^{18}-CS-NR^{19}R^{21}$ or $-(CH_2)_m-NR^{18}-CO-NR^{19}R^{21}$; or

E is $-CONR^{22}NR^{23}R^{24}$, wherein R^{22} is hydrogen, C_{1-6}–alkyl optionally substituted with one or more aryl or hetaryl, or aryl or hetaryl optionally substituted with one or more C_{1-6}–alkyl; R^{23} is C_{1-6}–alkyl optionally substituted with one or more aryl or hetaryl, or C_{1-7}–acyl; and R^{24} is hydrogen, C_{1-6}–alkyl optionally substituted with one or more aryl or hetaryl; or aryl or hetaryl optionally substituted with one or more C_{1-6}–alkyl; or

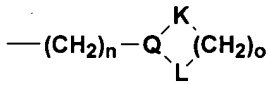
R^{22} and R^{23} together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more C_{1-6}–alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

R^{22} and R^{24} together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more C_{1-6}–alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

R^{23} and R^{24} together with the nitrogen atom to which they are attached may form a heterocyclic system optionally substituted with one or more C_{1-6}–alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

wherein m is 0, 1, 2, or 3,

R^{18}, R^{19} and R^{20} independently are hydrogen or C_{1-6}–alkyl optionally substituted with halogen, $-N(R^{25})R^{26}$, wherein R^{25} and R^{26} are independently hydrogen or C_{1-6}–alkyl; hydroxyl, C_{1-6}–alkoxy, C_{1-6}–alkoxycarbonyl, C_{1-6}–alkylcarbonyloxy or aryl;



wherein

Q is –CH< or –N<,

K and L are independently $-CH_2-$, –CO–, –O–, –S–, $-NR^{27}-$ or a valence bond,

where R^{27} is hydrogen or C_{1-6} alkyl;

n and o are independently 0, 1, 2, 3 or 4;

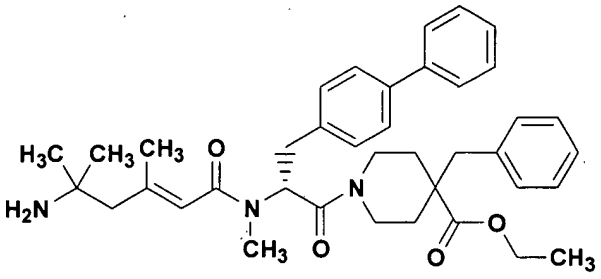
R^{20} is C_{1-6} alkyl, aryl or hetaryl;

or a pharmaceutically acceptable salt thereof;

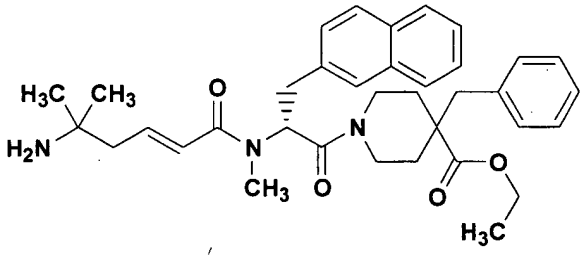
with the proviso that if M is a valence bond then E is $-CONR^{22}NR^{23}R^{24}$.

The Examiner specifically refers to Examples 10 to 13 which have the structures

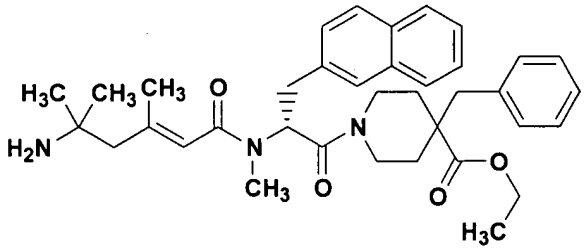
Example 10



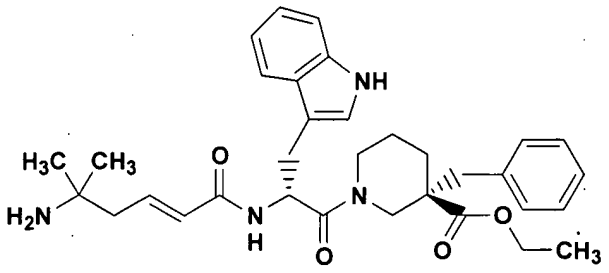
Example 11



Example 12



Example 13



It is submitted that Applicants' compounds as claimed are patentable over Hansen et al. The Hansen et al. compounds as shown in Formula I include the following moieties

$$-(CH_2)_d-J$$

and E attached to the nitrogen containing ring

d is 0, 1, 2 or 3

J is an aryl or a heteroaryl group and

E is

$-COR^{18}R^{19}$

$-COOR^{19}$

$-(CH_2)_m-NR^{18}SO_2R^{20}$

$-(CH_2)_m-NR^{18}COR^{20}$

$-(CH_2)_m-OR^{19}$,

$-(CH_2)_m-OCOR^{20}$,

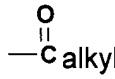
$-(CH)(R^{18})(R^{19})$,

$-(CH_2)_m-NR^{18}-CS-NR^{19}R^{21}$,

$-(CH_2)_m-NR^{18}-CO-NR^{19}R^{21}$,

$-CONR^{22}NR^{23}R^{24}$.

Please note that in Applicants' compounds as now claimed R_8 and R_9 are independently alkyl substituted with heteroaryl, cycloalkyl, aryl or $-C(=O)R_{13}$ where one of R_8 and R_9 is alkyl substituted with heteroaryl, and the other is cycloalkyl, or one of R_8 and R_9 is aryl and the other is



Hansen et al. does not disclose or suggest compounds where at least one of $-(CH_2)_d-J$ and E is cycloalkyl or –C(=O)alkyl. Thus, Hansen et al. does not disclose or suggest Applicants' compounds as now claimed regardless of whether $-(CH_2)_d-J$ and E are in the 3- or 4-position.

Accordingly, it is submitted that Applicants' compounds as claimed are patentable over Hansen et al.

The combination of Morriello et al. and Hansen et al. does not disclose or suggest Applicants' compounds as now claimed. Morriello only discloses piperidine substituted at the 3-position. Hansen et al. does not disclose or suggest the R_8 and R_9 cycloalkyl and alkanoyl substituents attached to the piperidine ring as claimed herein. Thus, the combination of Morriello et al. and Hansen et al. would not disclose or suggest Applicants' compounds as claimed or motivate one skilled in the art to modify Morriello et al.'s compounds to move the X and Y substituents to the 3-position to the 4-position of a piperidine ring. It could only be through the use of hindsight in view of Applicants' disclosure that one skilled in the art would modify the Morriello et al. compounds to move the X and Y substituents from the 3-position to the 4-position since there is nothing in either the Morriello et al. and Hansen et al. references which would suggest to one skilled in the art to make such a modification. This is especially true since Hansen et al. does not disclose or suggest a cycloalkyl or alkanoyl group attached to the N-containing ring.

Furthermore, absent the use of hindsight in view of Applicants' disclosure, one skilled in the art would have no reason to make such a combination. Morriello et al. is devoid of any compounds which include substituents at the 4-position of a piperidine ring. Hansen et al. is devoid of the cycloalkyl or alkanoyl groups required in Applicants' compounds. Thus, one skilled in the art, absent the use of Applicants' disclosure, would have no reason to combine these references since there is nothing in either reference which would suggest that such a combination be made and since even the combination would not disclose or suggest Applicants' compounds.

Both Morriello and Hansen teach compounds having growth hormone secretage ("GSH") activity useful in the treatment of growth-associated disorders. One of skill in the art of melanocortin receptor activity would not look to the structural variation of GSH compounds in order to design compounds having melanocortin receptor activity. In other words, <u>there is no motivation nor expectation of success</u> by one of skill in the art to design compounds having melanocortin activity simply based on the structural isomerism compounds known to have GSH activity.

Accordingly, Applicants' compounds are not obvious over Morriello in view of Hansen and it is requested that the Examiner's rejection of claims 1-5, 7-8, and 10-16 under 35 U.S.C. §103(a) be withdrawn.

Objections

Claim 17 has been drafted in independent form. Applicants believe the claim is now in condition for allowance.

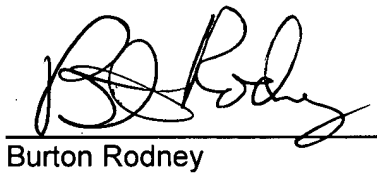
Summary

In view of the foregoing the Applicants believe that Claims 1, 3, 4, 6 to 8, 11 to 16, 18 to 22 and 23 to 27, as amended, are now in condition for allowance. The Examiner is invited to contact the undersigned by telephone, at the number listed below, if it is believed that a telephonic communication would facilitate the prosecution of this application.

Fees

If it is determined that a fee is due, please charge same to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

Respectfully submitted,



Burton Rodney
Attorney for Applicants
Reg. No. 22,076

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
609-252-4336

Date: May 10, 2004